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BEFORE THE BOARD OF PATENT APPEALS

AND INTERFERENCES

Paper No. 14

Application Number: 09/706683

Filing Date: 11/06/2000

Appellant(s): Childers et al.

Joseph M. Mazzarese

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 4/16/02.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief contains a statement that there are no related appeals or interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

There are only two issues for Appeal. Issue A , as enumerated by appellants, is limited to a how to use rejection for the scope claimed based on a very limited number of actual embodiments. Issue B is directed to a rejection under 35 USC 103 based on the teachings of Abou-Gharbia in view of Cliffe.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1,2,16 and 27-30 stand or fall together with respect to the rejection under 35 USC 112 and that claims 1-3 stand or fall together with respect to the rejection under 35 USC 103.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

5,254,552	Abou-Gharbia et al.	10/19/93
5,420,278	Cliffe	5/30/95

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

A. Claims 1,2,16,27-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are rejected based on an insufficient disclosure of how to use for scope claimed which entails heteroaryls both mono- and bicyclic at every R variable. Compounds made and tested are not representative of such a scope but rather of generic claim 3 as they are very homogeneous having almost always a phenyl at R1 and a 2-OMe phenyl at R2. Only 1 example of a heteroaryl is given, namely a pyrimidinyl corresponding to R2. See (R) and (S) isomer, egs.3 and 4. Specification discloses that **some** of the compounds are selective agonists or partial agonists while others

are antagonists on p.3 and again on pp.18-19 where limited test results are given. Having selective agonist/partial agonist activity vs. antagonistic activity will determine what uses can be treated as discussed in the background of the specification. For agonist activity, one can treat stroke and ischemia among other alleged uses as discussed in specification, p.3. Anxiety/depression it is stated can be treated with compounds having mixed profile of activity as discussed on p.1 and 3. Additional uses for antagonists are described on p.3. It remains the examiner's position that the amount of guidance presented in the specification as to which (het-substituted) compounds having the necessary $5HT_{1A}$ agonist and/or antagonist activity is minimal and consequently applicants' disclosure provides merely an invitation to those of ordinary skill in the art to determine which compounds have agonist activity, and which are antagonistic or a have a mixed profile of activity. In fact, compounds as diverse as the rings,ring systems embraced have not been shown **as a class** will have the minimum requisite activity needed to practice the invention and there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note US'552 applied below does not show such a scope at even one of the R locations. Note In re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also see

MPEP 2164.03 for enablement requirements in cases directed to structure-sensitive arts such as the pharmaceutical art.

In traversing the rejection appellants continue to ignore the reasoning , case law and state of the art as set out by the examiner but rather urge that applicants are not obligated to prepare and test each and every compound. True, but the examiner never required this . What the law does require is aptly stated in the following quote taken from Surrey at p.730:

"... where the applicant seeks to obtain a monopoly in exchange for his disclosure of a group of compounds there should be a disclosure which gives reasonable assurance that all,or substantially all of them are useful. ... An applicant is not entitled to a claim for a large group of compounds merely on the basis of a showing that a selected few are useful and a general suggestion of a similar utility in the others." . Later on the same page and following paragraph it was emphasized that reasonable assurance of asserted usefulness "as by adequate representative examples" had not been provided by appellants.

Furthermore, in traversing the 103 rejection below, appellants urge nature of activity (agonist v antagonistic) is not predictable. Applicants' own limited test data shows that this is not a predictable outcome just having the basic structural backbone. Eg.1 is antagonistic while its enantiomer is an agonist. Eg.3 (pyrimidyl derivative) is an agonist and its

enantiomer (eg.4) also is an agonist. Thus what might be the activity for the myriad of hetero-substituted compounds that can be present at any and all of R1-R3? Also binding data for 5HT1A receptor site covers a 30-fold range just for the limited data shown. Thus there is clear evidence that this a structure-sensitive art . MPEP 2164.03 not particularly addressed by appellants, states that where unpredictability is a factor such as in cases dealing with physiological activity, more than a single test result representative of a Markush member needs to be tested. Also the prior art, Abou-Gharbia (discussed below), does not assert all such rings only a few monocyclic azine rings at R2. Thus contrary to what appellants allege, ample reasoning based on the number of working examples, nature of invention which is unpredictable and lack of art-recognized equivalency have been relied on in making the present rejection which has not been adequately controverted by appellants.

B. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abou-Gharbia (US'552) in view of Cliffe (US '278) . The primary reference teaches similar compounds to that claimed herein for uses associated with binding to the 5 HT1A serotonin receptor site. These include the uses depression, and anxiety. Closest compounds in col.2 (2nd and 3rd species) differ only in lacking instant Y-R1 group .

Cliffe teaches for similar compounds and uses associated with serotonin antagonism the placement of phenyl groups (including substituted phenyl) on alkyl carbon **adjacent** to a number of nitrogen functional groups consisting of ureas, carbamates and carboxamide groups. See definition of R3 in cols.1-2 and X which includes -NR4COR6, the same functional group present in the primary reference and instant claims. Note that the alkylene chain connecting this group to the piperazine ring can be ethylene, also claimed herein and in the primary reference. Thus it would have been obvious to one skilled in the art at the time the invention was made to replace a hydrogen in "alpha" carbon of Abou-Gharbia's compounds with phenyl groups taught by Cliffe and in so doing obtain instant compounds (where Y= bond) with the expectation that they too would be useful as serotonin antagonists in view of the combined teachings outlined above.

In traversing the rejection appellants first urge that most of the compounds in US'552 differ in more than one respect while ignoring the two closest compounds pointed out by the examiner which differ only in lacking a phenyl group. The examiner is not obligated to rely on broader disclosures when narrower ones are also present in support of novelty or obviousness. Applicants' reasoning would lead to the requirement that **every** compound within a given reference would have to anticipate a given claim in order for it to be a 102 rejection but this is not the law. Second, while the amide linking group present in the instant

claims and in US'552, the primary reference, is not present in most of the species of Cliffe, the secondary reference was relied **only** on for showing the **one** feature of the instant invention not taught by Abou Gharbia, namely the R1 group, which is a preferred embodiment as stated in col.2, line 33 and present in most if not all of the working examples including eg.37, which is an example of a cycloalkylcarbonyl-N-ethylpiperazino carboxamide, the same structural features present in the primary reference and instant claims. Applicants seem to be ignoring that Cliffe is a secondary reference and not applied alone. The secondary reference is not believed to be dissimilar with the primary since it also deals with N-piperazinyl amides that permit a cycloalkyl of up to 12 carbons on the acyl carbon as exemplified by eg.37. By their very name, secondary references are expected to have some structural differences from what is instantly claimed otherwise they would be primary references or anticipations. Also they have common uses. The test for obviousness is not whether the elements of one reference can be bodily incorporated into the invention of another but rather what the combined teachings of the references would have suggested to those of ordinary skill in the art. Note In re Wood 202 USPQ 171. Given the references are from the same art area dealing with very similar compounds with the thrust of the teachings of Cliffe directed to **phenyl**-substituted alkylpiperazines of varying "X" containing groups the combination rejection is believed proper. Thus a fair reading of Abou-Gharbia when

combined with Cliffe would motivate one to modify compounds of the primary reference with (un)substituted phenyl on the carbon alpha to the nitrogen atom as was done herein.

Appellants further argue that there is no enablement for making instant phenyl-substituted compounds rendered obvious by the two references. The examiner pointed out that preparation via acylation is taught in both the primary and secondary references. See col.3 route (a) in Abou-Gharbia and col.5 and the working examples such as 2 and 3 which prepare the closest compounds pointed out above. Also see col.3 in Cliffe which employs acids,or acylating derivatives thereof to introduce the carboxamides. Thus the corresponding adamantyl acid chloride used in the examples of Abou-Gharbia coupled with the 1-phenylethyl amines (the one used in eg.37 of Cliffe was particularly pointed out to applicants as an example) of general formula shown in col.3, line 35 in Cliffe, which are both taught as readily available starting materials among other amines and acylating agents, would be readily apparent reagents of choice to prepare instant C-phenyl analogs as suggested by the combined art. This is consistent with appellants' own teaching in the specification on p.8 urging conventionality not novelty in preparing instant compounds. Thus there is ample direction in the prior art to make instant compounds following very standard reaction conditions-the same as relied on herein for making all of appellants' compounds not just those actually prepared.

Appellants' comment raised on p.10 of the brief, first full paragraph, is also not persuasive. It is not correct that appellants' compounds are solely taught as agonists/partial agonists for treating stroke. Specification clearly states some of the compounds are also antagonists (see p.19 for example) and the uses, anxiety and depression, are taught by **both of the applied** references based on 5HT1-A antagonistic activity making the references properly combinable.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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